Rejection under 35 U.S.C.§ 112, second paragraph

Claims 2 - 29, 31 - 50 and 52 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 22 - 27 and 52 have been cancelled, making the rejection under 35 U.S.C. § 112, second paragraph, moot. Claims 31- 50 have been amended. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(b)

Claims 23 - 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Hardman (U.S. Patent No. 4,939,666). Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 23 - 28 have been cancelled. Applicants respectfully request the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejection under 35 U.S.C. § 103 (a)

Claims 24 and 29 are rejected under 35 U.S.C. § 103(a) over Hardman in view of Lee (U.S. Patent No. 5,241,470). Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 24 and 29 have been cancelled. Applicants respectfully request the rejection under 35 U.S.C. § 103(a) be withdrawn.

DOUBLE PATENTING

Objection under 37 CFR 1.75

Claim 31 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 18. Without admitting the propriety of the rejection and reserving the right to pursue this claim at a later date, Claim 18 has been cancelled. Applicants respectfully request withdrawal of the rejection.

35 U.S.C. §101

Claims 2 - 10, 12 - 17 and 19 - 29 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 - 27 of co-pending Application 09/837,886. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2 - 10, 12 - 17 and 29 - 29 have been cancelled. Applicants respectfully request withdrawal of the rejection.

Claims 2 - 10 and 12 - 17 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 2 - 15 of prior U.S. Patent No. 6,188,965. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2 - 10 and 12 - 17 have been cancelled. Applicants respectfully request withdrawal of the rejection.

Claims 30 - 52 are rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1 - 23 of prior U.S. Patent No. 6,269,312. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 51- 52 have been cancelled; thus the rejection is moot as applied to these claims.

A statutory double patenting rejection is proper if the claims of an application are directed to the "same invention" as the claims in a patent that has already been granted to the Applicants, or that are in a co-pending application. *In re Vogel* states that:

> By "same invention" we mean identical subject matter. Thus the invention defined by a claim reciting "halogen" is not the same as that defined by a claim reciting "chlorine," because the former is broader than the latter.... A good test, and probably the only objective test, for "same invention," is whether one of the claims could be literally infringed without literally infringing the other. If it could be, the claims do not define identically the same invention.

Claims 30 –50 are not identical to cited Claims 1 - 23 of U.S. Patent No. 6,269,312 because they are directed to altering "amino acids" in contrast with "rotamers." As defined in the specification at page 7, lines 13 - 14, these are distinct:

> Each amino acid can be represented by a discrete set of all allowed conformers of each side chain, called rotamers.

Accordingly, Applicants respectfully withdrawal of the rejection of claims 30 - 50 based on double patenting with U.S. Patent No. 6,229,312.

Claim 18 is rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 2 of prior U.S. Patent No. 6,269,312. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claim 18 has been cancelled. Applicants respectfully request withdrawal of the rejection.

Non-statutory Double Patenting Rejection

Claim 2 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of U.S. Patent No. 6,188,965. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later

date, Claim 2 has been cancelled, making the obvious-type double patenting rejection based on Claim 2 of U.S. Patent No. 6,188,965 moot.

Claims 2, 6, 11, and 19–22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2, 6, 11, and 18 - 21 of U.S. Patent No. 6,269,312. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 2, 6, 11, and 19 -22 have all been cancelled, making the obvious-type double patenting rejection based on Claims 2, 6, 11 and 18 -21 of U.S. Patent No. 6, 269,312 moot.

Claims 6, 11, and 19 - 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6, 11, and 18 - 21 of U.S. Patent No. 6,269,312. Without admitting the propriety of the rejection and reserving the right to pursue these claims at a later date, Claims 6, 11, and 19 - 22 have all been cancelled, making the obvious-type double patenting rejection based on Claims 6, 11 and 18 - 21 of U.S. Patent No. 6, 269,312 moot.

The Applicants submit that in light of the above-amendment and argument, the claims are now in condition for allowance and an early notification of such is respectfully solicited.

Attached hereto is a marked-up version of the changes made to the claims by the "Amendment". The attached page is captioned **"Version with markings to show changes made."**

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 11/25/02

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 2 - 29, 51 and 52 have been canceled.

Claim 30 has been amended as shown below:

30. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure;

(C) establishing a group of potential amino acids for each of said variable residue positions; and

(D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized proteins sequences[, wherein said analyzing step includes a Dead-End Elimination (DEE) computation].

Claim 31 has been amended as shown below:

31. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acids;

(C) classifying each variable residue position as either a core, surface or boundary residue;

(D) [establishing a group of potential amino acids for each of said variable residue positions, wherein the group of potential amino acids for at least one of said variable residue positions has an amino acid selected from each of at least two different amino acids; and] establishing a group of potential amino acids for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains, and wherein a second group for a second variable position has a second set of at least two different amino acid side chains, and wherein said sets are different; and

(E) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

Claim 32 has been amended as shown below:

32. (Once Amended) A method according to claim 30, 31 or 53 wherein said analyzing step comprises a DEE computation.

Claim 33 has been amended as shown below

33. (Once Amended) A method according to claim [30 or 31] 30, 31 or 53 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

Claim 34 has been amended as shown below:

34. (Once Amended) A method according to claim [30 or 31] 32 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

Claim 35 has been amended as shown below:
35. (Once Amended) A method according to claim [30 or 31] 30, 31 or 53 wherein said analyzing step includes the use of at least one scoring function.

Claim 36 has been amended as shown below:
36. (Once Amended) A method according to claim 35 wherein said scoring function is selected from the group consisting of a [Van] van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

Claim 41 has been amended as shown below:
41. (Once Amended) A method according to claim [30 or 31] 30, 31 or 53 further comprising experimentally testing at least one member of said set.

42. (Once Amended) A method according to claim 33 further comprising the step of: generating a [rank ordered] list of additional optimal sequences from said globally optimal protein sequence.

Claim 45 has been amended as shown below:
45. (Once Amended) A method according to claim 42 further comprising the step of: testing some or all of said protein sequences from said [ordered] list to produce potential energy test results.

Claim 47 has been amended as shown below
47. (Once Amended) A recombinant protein comprising an optimized protein sequence generated by the method of claim [30 or 31] 30, 31 or 53.

Appendix of Pending Claims

30. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure;

(C) establishing a group of potential amino acids for each of said variable residue positions; and

(D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized proteins sequences.

31. (Once Amended) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acids;

(C) classifying each variable residue position as either a core, surface or boundary residue;

(D) establishing a group of potential amino acids for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains, and wherein a second group for a second variable position has a second set of at least two different amino acid side chains, and wherein said sets are different; and

(E) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

32. (Once Amended) A method according to claim 30, 31 or 53 wherein said analyzing step comprises a DEE computation.

33. (Once Amended) A method according to claim 30, 31 or 53 wherein said set of optimized protein sequences comprises the globally optimal protein sequence.

34. (Once Amended) A method according to claim 32 wherein said DEE computation is selected from the group consisting of original DEE and Goldstein DEE.

35. (Once Amended) A method according to claim 30, 31 or 53 wherein said analyzing step includes the use of at least one scoring function.

36. (Once Amended) A method according to claim 35 wherein said scoring function is selected from the group consisting of a van der Waals potential scoring function, a hydrogen bond potential scoring function, an atomic solvation scoring function, an electrostatic scoring function and a secondary structure propensity scoring function.

37. A method according to claim 35 wherein said analyzing step includes the use of at least two scoring functions.

38. A method according to claim 35 wherein said analyzing step includes the use of at least three scoring functions.

39. A method according to claim 35 wherein said analyzing step includes the use of at least four scoring functions.

40. A method according to claim 35 wherein said atomic solvation scoring function includes a scaling factor that compensates for over-counting.

41. (Once Amended) A method according to claim 30, 31 or 53 further comprising experimentally testing at least one member of said set.

42. (Once Amended) A method according to claim 33 further comprising the step of: generating a list of additional optimal sequences from said globally optimal protein sequence.

43. A method according to claim 42 wherein said generating includes the use of a Monte Carlo search.

44. A method according to claim 31 wherein said analyzing step comprises a Monte Carlo computation.

45. (Once Amended) A method according to claim 42 further comprising the step of: testing some or all of said protein sequences from said list to produce potential energy test results.

46. A method according to claim 45 further comprising the step of:
analyzing the correspondence between said potential energy test results and theoretical potential energy data.

47. (Once Amended) A recombinant protein comprising an optimized protein sequence generated by the method of claim 30, 31 or 53.

48. A nucleic acid sequence encoding a recombinant protein according to claim 47.

49. An expression vector comprising nucleic acid sequence of claim 48.

50. A host cell comprising the nucleic acid sequence of claim 48.

53. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

(A) receiving a protein backbone structure with variable residue positions;

(B) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential amino acids;

(C) establishing a group of potential amino acids for each of said variable residue positions, wherein a first group for a first variable position has a first set of at least two amino acid side chains, and wherein a second group for a second variable position has a second set of at least two different amino acid side chains; and

(D) analyzing the interaction of all or part of each of said amino acids with all or part of the remainder of said protein backbone structure to generate a set of optimized protein sequences.

54. (New) A method according to claim 53 wherein said first and second sets of amino acids are different.

55. (New) A method according to claim 53 wherein said first and second sets of amino acids are the same.

56. (New) A method executed by a computer under the control of a program, said computer including a memory for storing said program, said method comprising the steps of:

a) receiving a protein backbone structure with variable residue positions;
b) altering at least one supersecondary structure parameter value of said protein backbone structure prior to establishing a group of potential residue positions;
c) establishing a group of potential rotamers for each of said variable residue positions, wherein the group for at least one variable residue position has rotamers of at least two different amino acid side chains, and wherein at least one of said amino acid side chains is from a hydrophilic amino acid; and,
d) analyzing the interaction of each of said rotamers with all or part of the remainder of said protein to generate a set of optimized protein sequences, wherein said analyzing step includes the use of at least one scoring function.

57. (New) A method according to claim 56 wherein said first and second sets of rotamers are different.

58. (New) A method according to claim 56 wherein said first and second sets of rotamers are the same.

59. (New) A method according to claim 56 wherein said hydrophilic amino acid is selected from the group consisting of serine, threonine, aspartic acid, asparagine, glutamine, glutamic acid, arginine, lysine, and histidine.

60. (New) A method according to claims 53 - 59 further comprising physically generating at least one member of said set of optimized protein sequences and experimentally testing said sequence for a desired function.